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Chiral dimethyl(allyloxybenzo) pyridino-18-crown-6 (**9**, see Figure 1) was prepared for possible attachment to silica gel. The synthetic sequence requires the preparation of chiral dimethyl-substituted 2,6-bis(hydroxyethoxymethyl)pyridine (**20**, see Scheme I). Macrocycle **9** did not interact with an organic ammonium salt. Chiral allyloxydimethylpyridino-18-crown-6 (**8**), on the other hand, exhibited good recognition for one of the enantiomers of chiral α-(1-naphthyl)ethylammonium perchlorate.

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by

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Introduction

The design, synthesis and use of macrocycles capable of selective recognition of other molecules is of great interest to workers in many fields.[1-3] Our interest is in the area of enantiomeric recognition and has focused on the interactions of chiral crown macrocycles with chiral organic ammonium cations.[4-10] We have chosen interactions of the chiral pyridino-18-crown-6 ligands because they form relatively strong complexes with the organic ammonium salts[11] and they can be prepared in the laboratory with various substituents on chiral positions on the macroring. We have made a systematic study of how the extent of enantiomeric recognition varies with crown substitutent, guest type and solvent.[6,7,10]

Chiral pyridino-18-crown-6 ligands have been prepared with two methyl groups (compounds **1** and **2** in Figure 1)[4,12], two phenyl groups (**3** and **4**),[5,7] two *sec*-butyl groups (**5**)[6], and two *t*-butyl groups (**6** and **7**)[7] in chiral positions near the rigid pyridine portion of the macroring. These macrocycles were prepared by treating the relevant chiral dialkyl-substituted tetraethylene glycol with dimethyl 2,6-pyridinedicarboxylate or 2,6-pyridinedimethyl ditosylate. Chiral ligand **2** was prepared by a Raney nickel reduction of the corresponding dithiono-crown where X = S.[12] A number of other chiral dialkylpyridino-18-crown-6[6] and chiral triazolo-18-crown-6 ligands[13] have been prepared but they either did not exhibit significant enantiomeric recognition or their recognition properties have not been determined.

Compounds **1-7** interact with [α-(1-naphthyl)ethyl]ammonium (NapEt) perchlorate in a variety of solvent systems. This interaction has been studied by a

temperature dependent ^{1}H NMR technique to give the free energy of activation ($\Delta G_c^{\ddagger}$) for the dissociation of the complex.[4-7] The log *K* values for the interaction of the crown ligands with NapEtClO$_4$ have been determined by a direct ^{1}H NMR technique[8] and by a calorimetric titration method.[4,14] Log *K* values determined by these two methods were in good agreement.[8] Table I lists the enantiomeric recognition of these chiral ligands and others for the (*R*)- and (*S*)-forms of NapEtClO$_4$ as shown by $\Delta\Delta G_c^{\ddagger}$ and Δlog *K* values. It is interesting to note that Δlog K_c for the extraction of (*R*)- and (*S*)-NapEtClO$_4$ by **1** is 0.49[15] which is similar to the Δlog *K* value determined by the direct ^{1}H NMR technique (Table I). The calculated $\Delta\Delta G_c^{\ddagger}$ as determined by a force-field technique is very close, in most cases, to the observed $\Delta\Delta G_c^{\ddagger}$ as determined by the temperature dependent ^{1}H NMR method (Table I). It is obvious from the data in Table I that the best recognition was obtained when the two substituents were *t*-butyl or phenyl. Structures determined by X-ray crystallography[4,16] and by force-field calculations[6,7] show that the large alkyl or phenyl groups on the chiral host cause a larger steric repulsion in the (*S*,*S*)-host-(*S*)-guest than in the other diastereomeric complex.

We have also prepared a series of chiral diphenyl-substituted diazapyridino-18-crown-6 ligands (**10-13**).[10] Some interesting structural transformations of bis-*N*-methylthionoamido crown **17**, caused by the C(=S)N(CH$_3$)C*H(C$_6$H$_5$) portions of the molecule, were observed.[10] Only host molecules **10** and **12** gave measurable recognition for the enantiomers of NapEtClO$_4$ (see Table I).

We recently reported the synthesis of chiral allyloxypyridino-18-crown-6 (**8**) and

its attachment to silica gel (Our Technical Report No. 15).[17] Molecular models show that chiral allyloxybenzopyridino-18-crown-6 **9** should have the cavity size and should complex with ammonium salts. This report gives the synthesis of **9** and reports the complexation studies of **9** with NapEtClO$_4$

Allyloxybenzo-containing chiral glycol (**20**) needed for the synthesis of chiral allyloxy-substituted crown **9** was prepared as shown in Scheme I. 5-Allyloxy-1,3-benzenedimethyl ditosylate (**18**) was prepared by treating **17** with powdered KOH in THF followed by tosyl chloride. Care was taken to insure that the unstable benzyl tosylate moieties[18] were kept at a low temperature and **18** was used immediately to form **20** without a purification step. Chiral glycol **20** is stable and can be stored for an indefinite period of time. All intermediates and starting compounds were characterized by their IR and ^{1}H NMR spectra. No combustion analyses were carried out on these materials, however, a good elemental analysis was obtained on macrocycle **9** prepared from these new starting materials. New chiral macrocycle (*S,S*)-**9** was prepared as shown in Scheme II.

Allyloxy-substituted chiral crown **8** was found to interact strongly with (*R*)- and (*S*)-NapEtClO$_4$ in a $CDCl_3/CD_3OD$ (1/1) (v/v) mixture. The log *K* value for the interaction of (*S,S*)-**8** with (*R*)-NapEtClO$_4$ was 3.89 and that for (*S,S*)-**8** with (*S*)-NapEtClO$_4$ was 3.54 as determined by a direct ^{1}H NMR technique.[8] These values compare favorably with those for the interactions of parent chiral dimethylpyridino-18-crown-6 (**2**) with (*R*)- and (*S*)-NapEtClO$_4$ in the same solvent system. In the latter case, the log *K* values were 3.96 and 3.42.[19] Thus, the Δlog *K* value for chiral host-**8**

interactions are not as great as for parent chiral host **2** interactions (0.35 vs 0.54). Chiral host **8** was then attached to silica gel and the gel-bound host was found to separate NapEt into its enantiomeric forms (see Technical Report No. 15).

We prepared chiral (allyloxybenzo)pyridino-crown (*S,S*)-**9** to have a different site for attachment to silica gel. The X-ray structures of the solid (*R*)- and (*S*)-NapEtClO_4-**1** complexes clearly show that host-guest interactions are caused by hydrogen bonds between the ammonium hydrogens and pyridine nitrogen and the symmetrically spaced ring oxygen atoms.[4,16] Thus, the macroring oxygen atom opposite the pyridine ring is not involved so that a crown such as **9** with no heteroatom in that position could interact with an organic ammonium salt. Unfortunately, (*S,S*)- **9** did not interact with Nap$EtClO_4$ (see Table I) and, therefore, **9** will not be attached to silica gel.

Experimental

The ^{1}H NMR spectra were obtained at 200 MHz in $CDCl_3$ with TMS as the internal standard unless otherwise indicated. Melting points are uncorrected. Starting materials were used as purchased from Aldrich Chemical Company unless otherwise noted.

Dimethyl 5-Hydroxy-1,3-benzenedicarboxylate (15) (Scheme I). To a stirred mixture of 13.0 g (71.4 mmol) of 5-hydroxyisophthalic acid and 144 mL of CH_3OH in an ice-salt bath under Ar was slowly added 29 mL (47.3 g, 398 mmol) of thionyl chloride. After addition, the reaction mixture was stirred in an ice-salt bath for 1 h then at rt for 16 h. The reaction mixture was condensed to 40 mL and stored in a refrigerator for 1 day. The white crystals were filtered and dried in a vacuum

dessicator over KOH pellets. After recrystallization from methanol, 14.3 g (95%) of pure **15** was obtained; 162-163 °C (lit.[21] mp 159-160 °C); ^{1}H NMR δ 3.88 (s, 6 H), 7.56 (s, 2 H), 7.92 (s, 1 H), 10.30 (s, 1 H, disappeared in D_2O).

Dimethyl 5-Allyloxy-1,3-benzenedicarboxylate (16) (Scheme I). To a stirred solution of 0.82 g (35.7 mmol) of sodium metal in 50 mL of dry and pure CH_3OH was added 5.0 g (23.8 mmol) of **15** in portions under Ar. The reaction mixture was stirred for 10 min and then 7.5 mL (10.5 g, 86.7 mmol) of allyl bromide was added. After stirring the reaction mixture at rt for 10 min, it was refluxed for 2 days. The solvent was evaporated under reduced pressure. The residue was dissolved in a cold mixture of 100 mL of 5% NaOH and 250 mL of CH_2Cl_2. The phases were shaken well and separated. The aqueous phase was shaken with two 100-mL portions of CH_2Cl_2. The combined organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude solid material was recrystallized from CH_3OH to give 5.24 g (88%) of pure **16**; mp 71-72 °C; IR (KBr) 3089, 3048, 3031, 1723, 1595, 1435, 1344, 1248, 1115, 1043, 1011 cm^{-1}; ^{1}H NMR δ 3.92 (s, 6 H), 4.58-4.68 (m, 2 H), 5.24-5.54 (m, 2 H), 5.92-6.16 (m, 1 H), 7.75 (s, 2 H), 8.25 (s, 1 H).

5-Allyloxy-1,3-benzenedimethanol (17) (Scheme I). To a stirred suspension of 1.21 g (32 mmol) of $LiAlH_4$ in 20 mL of pure and dry ether under Ar was added dropwise at 0 °C, a solution of 4.0 g (16 mmol) of **16** dissolved in 80 mL of ether. After addition of the diester, the reaction mixture was stirred at 0 °C for 1 h, at rt for 18 h and at reflux temperature for 6 h. The reaction mixture was cooled to 0 °C and 1.3 mL of a saturated aqueous NH_4Cl solution was slowly added. Then 2.6 mL of 5% aqueous NaOH solution was added. The resulting mixture was stirred at 0 °C for

10 min, at rt for 30 min and at reflux temperature for 16 h. After the reaction mixture was cooled to rt, the white precipitate was filtered and washed three times with 50-mL portions of ether. The ethereal filtrate and washings were combined, dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure. The resulting white solid was recrystallized from ether to give 2.64 g (85%) of **17** as white crystals; mp 56-58 °C; IR (KBr) 3356, 3030, 1610, 1597, 1423, 1366, 1299, 1168, 1047, 989, 953, 874, 853, 708, 660 cm^{-1}; ^1H NMR δ 3.35 (t, 2 H, J = 6 Hz, disappeared in D_2O), 4.40-4.48 (m, 2 H), 4.50 (t, 4 H, J = 6 Hz), 5.20-5.45 (m, 2 H), 5.9-6.13 (m), 6.72 (s, 2 H), 6.82 (s, 1 H).

5-Allyloxy-1,3-benzenedimethyl Ditosylate (18) (Scheme I). To a vigorously stirred suspension of 3.95 g (61.7 mmol, 87.6% assay) of finely powdered KOH in 20 mL of pure and dry THF at 0 °C under Ar was added 2.65 g (13.6 mmol) of **17** dissolved in 50 mL of THF. Then, 6.5 g (34 mmol) of TsCl dissolved in 40 mL of THF was added dropwise. The reaction mixture was stirred at 0 °C for 4 h. By that time, the TLC analysis showed the disappearance of both the starting alcohol and tosyl chloride and the appearance of a single spot at R_f = 0.8 [silica gel, eluant = CH_3OH/toluene (1/4)]. Isolation of **18** was done rapidly and at low temperature because the benzyl tosylates are known to be unstable at rt.[18] After the reaction was completed, the solvent was evaporated under reduced pressure and the residue was dissolved in a mixture of 200 mL of CH_2Cl_2, 50 g of ice and 40 mL of water. The phases were shaken well and separated. The aqueous phase was shaken with 200 mL of CH_2Cl_2. The combined organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give 6.63 g (97%) of an oil which

was immediately used in the next step without further purification; IR (neat) 3090, 3069, 3034, 1599, 1494, 1478, 1456, 1360, 1189, 1177, 1096, 933 cm^{-1}; ^1H NMR δ 2.44 (s, 6 H), 4.38-4.51 (m, 2 H), 4.94 (s, 4 H), 5.21-5.48 (m, 2 H), 5.88-6.12 (m, 1 H), 6.68 (s, 1 H), 6.72 (s, 2 H), 7.32 (d, 4 H, J = 10 Hz), 7.78 (d, 4 H, J = 10 Hz).

5-Allyloxy-1,3-bis(4-hydroxy-3*S*-(+)-methyl-2-oxabutyl)benzene (20) (Scheme I). To a stirred suspension of 1.21 g (40.3 mmol, 80% dispersion in mineral oil) of NaH in 10 mL of dry and pure THF was added dropwise at 0 °C under Ar 4.61 g (28.8 mmol) of (*S*)-(-)-2-(tetrahydropyranyloxy)propanol (**19**)[10] dissolved in THF. The reaction mixture was stirred at 0 °C for 10 min, at rt for 10 min and at reflux temperature for 3 h. The reaction mixture was cooled to 0 °C, and 6.03 g (12 mmol) of **18**, dissolved in 50 mL of THF, was added over a 3-min period. The reaction mixture was stirred at 0 °C for 20 min, then at rt for 2 days and the solvent was evaporated under reduced pressure. The residue was dissolved in a mixture of 250 mL of CH_2Cl_2, 60 g of ice and 30 mL of water. The mixture was shaken well and separated. The aqueous phase was shaken two times with 100-mL portions of CH_2Cl_2. The combined organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to give 5.7 g (99%) of THP blocked glycol. To the latter material was added a mixture of 1 mL of concentrated aqueous HCl and 100 mL of CH_3OH and the mixture was stirred at rt for 4 h. Na_2CO_3 (2.7 g) was added and the mixture was stirred overnight. The solvent was evaporated under reduced pressure and the residue was dissolved in a mixture of 200 mL of CH_2Cl_2 and 150 mL of water. The phases were mixed well and separated. The aqueous phase was shaken two times with 50-mL portions of CH_2Cl_2. The combined organic phase was

dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel using acetone/benzene (1/4) as eluent to give 2.55 g (69%) of **20** as an oil; $[\alpha]_D^{22}$ + 16.51° (c = 2.75, $CHCl_3$); IR (neat) 3418, 3081, 1648, 1598, 1455, 1371, 1296, 1157, 1097, 1056, 1003, 930, 849; ^1H NMR δ 1.12 (d, 6 H, J = 6 Hz), 2.71 (s, 2 H, broad, disappeared in D_2O), 3.22-3.46 (m, 4 H), 3.92-4.01 (m, 2 H), 4.49 (s, 4 H), 4.50-4.55 (m, 2 H), 5.23-5.43 (m, 2 H), 5.92-6.11 (m, 1 H), 6.81 (s, 2 H), 6.86 (s, 1 H); MS (low volt) m/e 310 (M^+).

10-Allyoxy-(4*S*,16*S*)-(+)-4,16-dimethyl-3,6,14,17-tetraoxa-23-aza-tricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8,10,12,19,21-hexaene (*S*,*S*-9) (Scheme II). To a *stirred suspension of 0.61 g (20 mmol, 80% dispersion in mineral oil)* of NaH in 20 mL of pure and dry THF was added dropwise at 0 °C and under Ar a solution of 2.23 g (7.18 mmol) of *S*,*S*-**20** dissolved in 120 mL of THF. The reaction mixture was stirred at 0 °C for 10 min, at rt for 10 min and at reflux for 3 h. The mixture was cooled to 0 °C and 3.55 g (7.93 mmol) of **21** dissolved in 120 mL of THF was added dropwise. After stirring the reaction mixture at 0 °C for 10 min, it was stirred at rt for 2 days. When the reaction was completed, the solvent was evaporated under reduced pressure. The residue was dissolved in a mixture of 200 mL of CH_2Cl_2, 40 g of ice and 100 mL of water. The phases were shaken well and separated. The aqueous phase was shaken twice with 100-mL portions of CH_2Cl_2. The combined organic phase was dried ($MgSO_4$), filtered and the solvent was removed under reduced

pressure. The residue was purified by chromatography on neutral alumina using toluene and C_2H_5OH/toluene (1/200) as eluents to give 1.37 g (46%) of **9** as a white solid; mp 48-49 °C; $[\alpha]_D^{22}$ + 48.61° (c = 2.119, $CHCl_3$); IR (KBr) 3063, 1646, 1615, 1595, 1578, 1452, 1426, 1360, 1289, 1255, 1225, 1108, 1116, 1055, 1020, 1006, 863 cm^{-1}; ^1H NMR δ 1.22 (d, 6 H, J = 6 Hz), 3.44-3.59 (m, 4 H), 3.7-3.91 (m, 2 H), 4.3-4.56 (m, 6 H), 4.65-4.81 (m, 4 H), 5.2-5.46 (m, 2 H), 5.91-6.14 (m, 1 H), 6.7 (s, 2 H), 7.0 (s, 1 H), 7.27 (d, 2 H, J = 8 Hz), 7.64 (t, 1 H, J = 8 Hz); MS (low voltage) m/e 413 (M^+); Anal. Calcd. for $C_{24}H_{31}NO_5$: C, 69.71; H, 7.56. Found: C, 69.99; H, 7.67.

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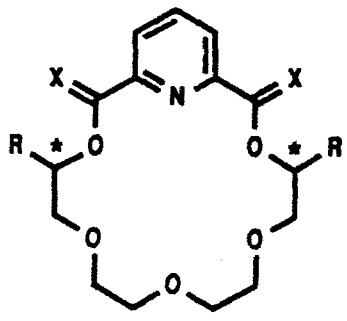
Table I. Recognition of the Enantiomers of Chiral [α-(1-Naphthyl)ethyl]ammonium Perchlorate by Various Chiral Pyridino-18-crown-6 Ligands as Measured by Differences in the Free Energies of Activation ($\Delta\Delta G_c^{\ddagger}$) (kcal/mole) or Differences in Log *K* values (ΔLog *K*) for Their Interactions in CD_2Cl_2 ($\Delta\Delta G_c^{\ddagger}$ Values) or in Mixtures of CD_3OD (M) and $CDCl_3$ (C) (Δlog *K* Values)

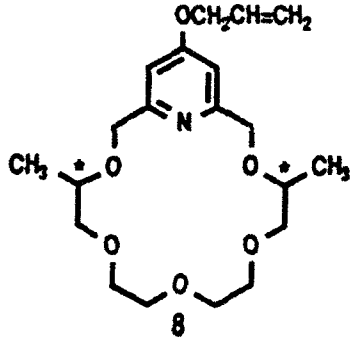
	$\Delta\Delta G_c^{\ddagger}$		
Ligand	Observed	Calculated	ΔLog *K*
(S,S)-1	1.1[a]	0.7[b]	0.6 (5M/5C)[c,d]
(S,S)-2	1.6[a]	1.7[b]	0.54 (5M/5C)[c,e]
(S,S)-3	1.3[b]	2.5[b]	>0.85 (7M/3C)[c,f]
(R,R)-4	2.8[e]		0.28 (M)[c,f]
(R,R)-5	0.8[b]	1.7[b]	
(S,S)-6	>1.8[f]	2.5[b]	NR[c,f]
(S,S)-7	2.5[f]	2.2[b]	0.71 (1M/9C)[c,f]
(S,S)-8			0.35 (5M/5C)[c,d]
(S,S)-9			NR (5M/5C)[g]
(S,S)-10			0.37 (5M/5C)[c,h]
(S,S)-11	0.1[h]		
(S,S)-12	0.1[h]		0.2 (5M/5C)[c,h]
(S,S)-13	0.1[h]		0.1 (5M/5C)[c,h]

[a]Reference 4. [b]Reference 6. [c]Determined by an ^1H NMR technique.[8] [d]Reference 31. [e]Reference 24. [g]Determined by a calorimetric method.[14] [h]Reference 10.

Figure 1. Chiral Pyridino-18-crown-6 Ligands



1, X = O, R = CH_3
2, X = H_2, R = CH_3
3, X = O, R = C_6H_5
4, X = H_2, R = C_6H_5
5, X = O, R = *s*-C_4H_9
6, X = O, R = *t*-C_4H_9
7, X = H_2, R = *t*-C_4H_9



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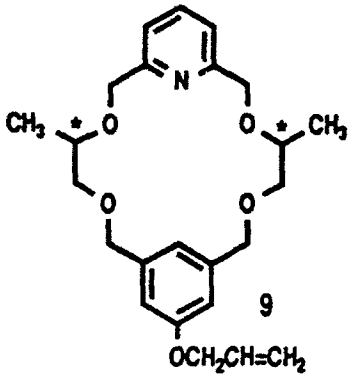

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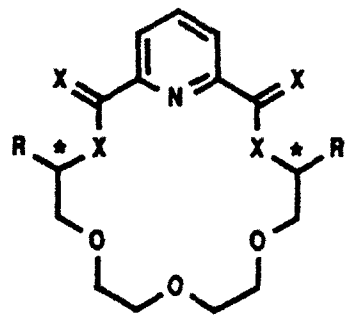
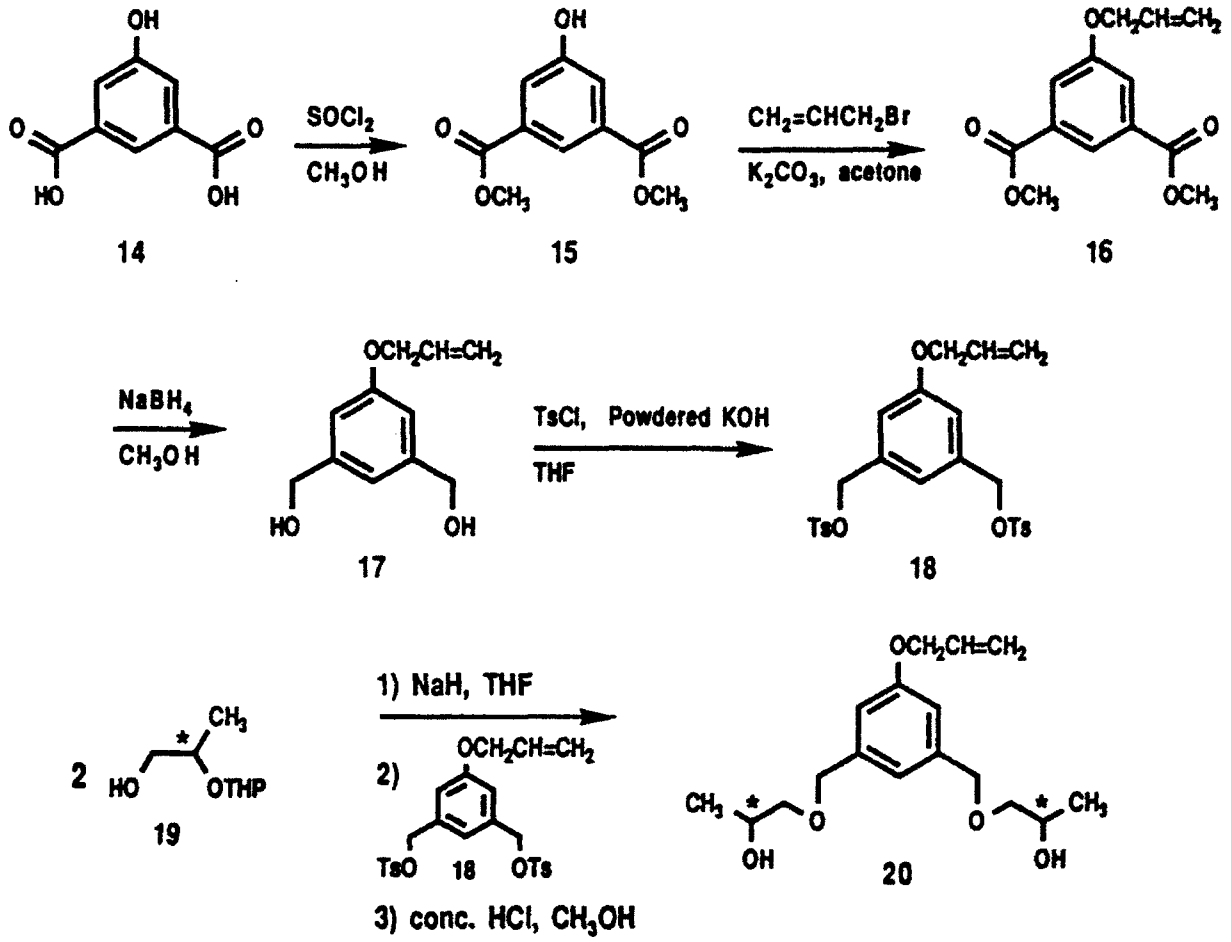


10, X = NH; Y = S; R = phenyl
11, X = NCH_3; Y = O; R = phenyl
12, X = NCH_3; Y = S; R = phenyl
13, X = NCH_3; Y = H_2; R = phenyl

Scheme I. Preparation of 3-Allyloxy-1,5-benzenedimethyl Ditosylate (18) and Chiral Allyloxybenzoglycol (20)



Scheme II. Preparation of Chiral (Allyloxybenzo)pyridino Crown 9